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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/246,129 | 02/08/1999 | GUO-LIANG YU | PF141P4 | 5810 |

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|---|---|
| ROMEO, DAVID S | |

| ART UNIT | PAPER NUMBER |
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| 1647 | 28 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/246,129 | Applicant(s) YU ET AL. | |
|---|---|---|---|
| | Examiner David S Romeo | Art Unit 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *42-48,52-56,59,62-66,69,72-77,80,83,86-89 and 92-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

4/16/03 5)☒ Claim(s) *65,66 and 72-74* is/are allowed.

6)☒ Claim(s) *42,48,52-56,59,62-64,75,76,86-89 and 92-94* is/are rejected.

7)☒ Claim(s) *43-47,77,80 and 83* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *27* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

The amendment filed January 21, 2003 (Paper No. 26) has been entered. Claims 42-48, 52-56, 59, 62-66, 69, 72-77, 80, 83, 86-89, 92-94 are pending and being examined.

***Maintained Formal Matters, Objections, and/or Rejections:***

***Claim Rejections - 35 USC § 112***

Claims 55, 56, 59, 62-64, 75, 76, 86-89, 92-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to or encompass a genus of polypeptides that are at least 90 or 95 per cent identical to SEQ ID NO: 2 or to some portion of SEQ ID NO: 2 and a genus of polypeptides encoded by a genus of nucleic acid molecules that hybridize to the complement of SEQ ID NO: 1. In the case of the former there are no functional limitations to the polypeptides. In the case of the latter the polypeptides have proinflammatory activity.

Applicant argues that the examiner has not met his burden and that the inventor has possession of the claimed invention based on the specification as filed. Applicant's arguments have been fully considered but they are not persuasive. The specification, as filed, indicates that the polypeptide of the present invention has been identified as a novel member of the TNF family based on structural, amino acid sequence homology, and functional similarities, for example, TNF-gamma is a pro-inflammatory protein. page 3. TNF-gamma does not bind significantly to two soluble TNF receptors, sTNF-RI (p55) and sTNF-RII (p75). Accordingly,

TNF-gamma may have activities inclusive of and additional to known TNF proteins (see FIG. 13). See page 93, lines 31-33. As noted above, in some cases there are no functional limitations to the polypeptides. The absence of a functional limitation encompasses any and all functions, including activities inclusive of and additional to known TNF proteins. The claims encompass polypeptides of unknown and undescribed function. There is a lack of written description of the genus because polypeptides of unknown and undescribed function are not adequately described in the present application's specification. There is a lack of written description of the genus because polypeptides of unknown and undescribed function do not describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention and do not describe distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. A genus of biomolecule sequences described only by a structural characteristic, i.e., per cent identity, without any known or disclosed correlation between that structural genus and the function of the genus, is not a sufficient identifying characteristic for written description purposes in this case because there is no known or disclosed method of obtaining unknown and undescribed functional activities additional to known TNF proteins. A lack of adequate written description issue also arises because the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage unknown and undescribed functional activities additional to known TNF proteins. Nor does a "laundry list" disclosure of every conceivable activity constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species with a particular activity. The Federal Circuit has pointed out that under United States law, a description that does not render a

claimed invention obvious cannot sufficiently describe the invention for the purposes of the written description requirement of 35 U.S.C. 112. Lack of a functional limitation does not clearly convey the information that an applicant has invented the subject matter which is claimed and does not put the public in possession of what the applicant claims as the invention. The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. Clearly, Applicant was not in possession of unknown and undescribed functional activities additional to known TNF proteins.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The present application exemplifies two species, i.e., TNF-γ-α and TNF-γ-β. TNF-γ-α (or VEGIα for Vascular Endothelial derived tumor Growth Inhibitor alpha) exhibited 20-30% sequence homology to other members of the TNF family. Subsequent database analysis and library screening identified a novel splicing variant of TNF-gamma-alpha, designated TNF-gamma-beta

(or VEGIβ). The cDNA for TNF-gamma-alpha encodes 174 amino acid residues and TNF-gamma-beta encodes 251 amino acids. Both proteins have characteristics of type II transmembrane proteins. They only differ at the N-terminus which corresponds to the intracellular and transmembrane domains (FIGS. 18A-D and 19). See page 118. Two protein species that differ only at the N-terminus does not reflect the variation within the claimed genus because the genus encompasses polypeptides of unknown and undescribed functional activities additional to known TNF proteins that differ anywhere and everywhere from TNF-γ-α (SEQ ID NO: 2). What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, first paragraph.

Union Oil of Cal. v. Atlantic Richfield Co., 208 F.3d 989, 54 USPQ2d 1227, (Fed. Cir. 2000) is inapposite because unlike the cited case wherein description in terms of ranges of chemical properties which work in combination with ranges of other chemical properties to produce an automotive gasoline that reduces emissions was found to provide an adequate written description even though the exact chemical components of each combination were not disclosed and the specification did not disclose any distinct embodiments corresponding to any claim at

issue, in the present case a genus of biomolecule sequences described only by a structural characteristic, i.e., per cent identity, without any known or disclosed correlation between that structural genus and the function of the genus, is not a sufficient identifying characteristic for written description purposes because there is no known or disclosed method of obtaining unknown and undescribed functional activities additional to known TNF proteins.

According to Stedman's Medical Dictionary 27th Edition (u28), inflammation is a fundamental pathologic process consisting of a dynamic complex of cytologic and chemical reactions that occur in the affected blood vessels and adjacent tissues in response to an injury or abnormal stimulation caused by a physical, chemical, or biologic agent, including: 1) the local reactions and resulting morphologic changes, 2) the destruction or removal of the injurious material, 3) the responses that lead to repair and healing. The so-called "cardinal signs" of i. are: rubor, redness; calor, heat (or warmth); tumor, swelling; and dolor, pain; a fifth sign, functio laesa, inhibited or lost function, is sometimes added. All of the signs may be observed in certain instances, but no one of them is necessarily always present. However, the present application does not describe an assay with which proinflammatory activity could be assayed. In addition, the present specification also indicates that since TNF-gamma-alpha and/or TNF-gamma-beta inhibit immune cell functions, it will have a wide range of anti-inflammatory activities (page 88, lines 14-17). A "laundry list" disclosure of every conceivable activity, i.e., proinflammatory activity and anti-inflammatory activities does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species with a particular activity.

The rejection of claims 55, 56, 59, 62-64 is maintained because there is confusion over the metes and bounds of these claims. See below.

***Specification***

The amendment filed September 26, 2001 (Paper No. 18) is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "U034070" in the paragraph bridging lines 20-27 at page 10. Applicant argues that "U034070" is a GenBank identifier. Applicant's arguments have been fully considered but they are not persuasive. "U034070" does not identify any entry in GenBank.

Applicant is required to cancel the new matter in the reply to this Office Action.

***New formal matters, objections, and/or rejections:***

***Claim Rejections - 35 USC § 112***

Claims 89, 92-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed to a genus of polypeptides encoded by a genus of nucleic acid molecules that hybridize to the complement of SEQ ID NO: 1, wherein the genus of polypeptides have proinflammatory activity. According to Stedman's Medical Dictionary 27th Edition (u28), inflammation is a fundamental pathologic process consisting of a dynamic complex of cytologic

and chemical reactions that occur in the affected blood vessels and adjacent tissues in response to an injury or abnormal stimulation caused by a physical, chemical, or biologic agent, including: 1) the local reactions and resulting morphologic changes, 2) the destruction or removal of the injurious material, 3) the responses that lead to repair and healing. The so-called "cardinal signs" of i. are: rubor, redness; calor, heat (or warmth); tumor, swelling; and dolor, pain; a fifth sign, functio laesa, inhibited or lost function, is sometimes added. All of the signs may be observed in certain instances, but no one of them is necessarily always present. However, the present application does not describe an assay with which proinflammatory activity could be assayed. In addition, the present specification also indicates that since TNF-gamma-alpha and/or TNF-gamma-beta inhibit immune cell functions, it will have a wide range of anti-inflammatory activities. page 88, lines 14-17. The scope of the claims does not bear a reasonable correlation to scope of the disclosure because present application only exemplifies two species, i.e., TNF-γ-α and TNF-γ-β, that are splice variants and that only differ at the N-terminus (page 118) whereas the claims encompass polypeptides of unknown and undescribed functional activities additional to known TNF proteins that differ anywhere and everywhere from TNF-γ-α (SEQ ID NO: 2). The specification lacks working examples of and guidance for making variants that have proinflammatory activity to the exclusion of those that have a wide range of anti-inflammatory activities. The skilled artisan is left to extensive experimentation wherein variants are randomly made and through trail and error experimentation is left to determine which reaction in a dynamic complex of cytologic and chemical reactions is suitable for obtaining a variant with a desired activity. Moreover, there is a lack of predictability in the art. Predicting structure, hence function, from primary amino acid sequence data is extremely complex and there doesn't exist an

efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. See Bowie (v28) page 1306, column 1, full paragraph 1, or Ngo (x28) page 433, full paragraph 1, and page 492, full paragraph 2. In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 42, 48, 52, 53, 54 are indefinite over the recitation of "a polypeptide having the amino acid sequence expressed by a recombinant cell" because there are at least two forms (TNF-γ-α and TNF-γ-β) expressed by a cell. It is unclear which form is intended. The instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "a polypeptide having the amino acid sequence expressed by a recombinant cell" an artisan cannot determine what additional or material limitations are placed upon a claim by the presence of this element. The metes and bounds are not clearly set forth.

Claims 55, 56, 59, 62-64 are indefinite because the claims encompass a nucleic acid molecule consisting of a polynucleotide sequence of at least 30 contiguous nucleotides a DNA molecule and it is unclear if "of at least" is intended to mean "consisting of" or "comprising". It is unclear if the nucleic acid molecule consists of or comprises at least 30 contiguous

nucleotides. The metes and bounds are not clearly set forth. See claim 65 for a suggested claim construction.

***Conclusion***

Claims 43-47, 77, 80, 83 are objected to as being dependent upon a rejected base claim.

4/24/07 Claims 65, 66, 69, 72-74 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

BEFORE FINAL (703) 872-9306
AFTER FINAL (703) 872-9307

IN ADDITION TO THE OFFICIAL RIGHTFAX NUMBERS ABOVE, THE TC 1600 FAX CENTER HAS THE FOLLOWING OFFICIAL FAX NUMBERS: (703) 305-3592, (703) 308-4242 AND (703) 305-3014.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

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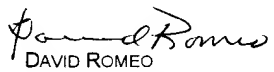

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APRIL 6, 2003